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EXAMINER
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DUFFY, BRADLEY

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1643

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/579,107	<b>Applicant(s)</b> VOLLMERS ET AL.	
	<b>Examiner</b> BRADLEY DUFFY	<b>Art Unit</b> 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 25 April 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 21-23,27-32,35,47 and 89-96 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 21-23,27-32,35,47 and 89-96 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 12 May 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)                 |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____  |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application       |
| Paper No(s)/Mail Date <u>3/16/2007</u> .   | 6) <input checked="" type="checkbox"/> Other: <u>Exhibits A and B</u> . |

### **DETAILED ACTION**

1. The election with traverse filed April 25, 2008, is acknowledged and has been entered.

Applicant has elected the invention of Group I.

2. The amendment filed April 25, 2008, is acknowledged and has been entered. Claims 21-23, 27-32, 35 and 47 have been amended. Claims 33, 36, 37 and 42-45 have been cancelled. Claims 89-96 are newly added.

3. Due to the rejoinder of Groups I-II detailed below, claims 21-23, 27-32, 35, 47 and 89-96 are pending in the application and are under examination.

### ***Election/Restrictions***

4. Upon further consideration of the restriction and election requirement set forth in the Office action mailed March 25, 2008, claims drawn to the inventions of Group II have been rejoined with claims drawn to the elected invention. The restriction and election requirement separating these inventions has been withdrawn. Notably, at page 18, lines 9-16, the specification teaches that the amino acid sequence of SEQ ID NO:5 is the heavy chain variable domain sequence of an antibody designated NORM-2 and that SEQ ID NO:7 is the light chain domain sequence of an antibody designated NORM-2.

5. Applicant's traversal of the restriction and election requirement set forth in the Office action mailed April 25, 2008, is acknowledged.

Applicant's arguments are moot in light of the rejoinder.

***Information Disclosure Statement***

6. The references cited in the information disclosure statement filed on March 16, 2007, have been considered. Notably, while considered, document FFR was crossed because it does not properly identify the document as a published document and therefore does not conform to the information disclosure statement requirements. (See MPEP 609).

***Priority***

7. Applicant's claim under 35 USC §§ 119 and/or 120 for benefit of the earlier filing date of US provisional application, 60/519,550, filed June 14, 2002, is acknowledged.

However, claims 21-23, 27-32, 35, 47 and 89-96 do not properly benefit under 35 U.S.C. §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under 35 USC §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Furthermore, claims 21-23, 28-32, 35, 47 and 89-95 do not properly benefit by the earlier filing because, because the prior application do not contain written support for the claims for the reasons set forth in the below rejection of the instant claims as containing NEW MATTER.

Accordingly, the effective filing date of the claims is deemed the filing date of PCT/IB04/04453, namely November 12, 2004.

### ***Specification***

8. The disclosure is objected to because of the following informalities:

a. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of such an improperly demarcated trademark appearing in the specification is TAXOL® (see, e.g., page 29, line 23).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., <sup>TM</sup>, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at <http://www.uspto.gov/web/menu/search.html>.

b. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 21-23, 27-32, 35, 47 and 89-96 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 21-23, 27-32, 35, 47 and 89-96 are indefinite in the recitation of “functional fragment”. This recitation renders the claim indefinite because antibodies are known to have multiple functions and it is unclear to which function the claim is directed. For example, must the functional fragment bind an Fc receptor, bind an antigen, decrease proliferation, induce apoptosis, cause ADCC or must the fragment have some other function? Which of the plurality of functions must the fragment have? The claims cannot be construed unambiguously without knowing the answer to this question. Thus, the claim fails to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

Accordingly, these claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(b) Claim 47 is also indefinite for the recitation of “said polypeptide”, because claim 21 and 27 only refer to an antibody or a functional fragment thereof. Accordingly, there is no antecedent basis in claims 21 or 27 to support this recitation in claim 47. Because of the ambiguity that results from the lack of antecedent basis supporting the recitation, it is unclear which (if any) “polypeptide” is being referred to in claim 47. Notably, the recited cell line expresses, i.e., produces, many different polypeptides and therefore, it is unclear which polypeptide is being referred to. For these reasons, the claim fails to delineate the metes and bounds of the subject matter regarded as the invention with the clarity and particularity necessary to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

Accordingly, this claim is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

### ***Claim Rejections - 35 USC § 112***

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

Art Unit: 1643

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 21-23, 27-32, 35, 47 and 89-96 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, "Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

Furthermore, the Federal Circuit has commented that each case involving the issue of written description, “must be decided on its own facts. Thus, the precedential value of cases in this area is extremely limited.” *Vas-Cath*, 935 F.2d at 1562 (quoting *In re Driscoll*, 562 F.2d 1245, 1250 (C.C.P.A. 1977)). See *Noelle v. Lederman*, 69 USPQ2d 1508 (CAFC 2004).

Finally, with further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsius verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

*Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also*: *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention*.

In the instant case, the claims are drawn to a structurally and functionally diverse genus of “antibodies or functional fragments thereof”, such as an antibody comprising a heavy chain variable region with at least 80% identity to the amino acid sequence of SEQ ID NO:5 and a light chain variable region with at least 80% identity to the amino acid sequence of SEQ ID NO:7, wherein the antibody specifically binds to an adenocarcinoma of the colon, a diffuse-type stomach carcinoma, an adenocarcinoma of the pancreas, or an adenocarcinoma of the lung, or a functional fragment thereof which specifically binds to an adenocarcinoma of the colon, a diffuse-type stomach carcinoma, an adenocarcinoma of the pancreas, or an adenocarcinoma of the lung (see claim 21)

Art Unit: 1643

or an antibody comprising amino acids 31-35, 50-66, and 99-108 of SEQ ID NO:5 or amino acids 23-36, 52-58, and 91-101 of SEQ ID NO:7 or a functional fragment thereof (see claim 27). Notably, because claim 32 recites that said functional fragment of claim 21 or claim 27 can be an Fc domain, which would not comprise a variable light chain domain or a variable heavy chain domain, it is apparent that the "functional fragment thereof" of claim 21 and claim 27 is not required to comprise any amino acid sequence of SEQ ID NO:5 or 7. Further dependent claims set forth other percent identities that the antibody must have when compared to SEQ ID NOs:5 and/or 7 (see claims 22, 23, 89, 90, 91 and 92), that the antibody or functional fragment thereof induces apoptosis (claim 93) or decreases proliferation (claim 94) of any one of Colo-699 (DSMZ Accession Number ACC 196), CACO-2 (DSMZ Accession Number ACC169, ATCC Accession Number HTB-37), 23132/87 (DSMZ Accession Number ACC 201), DU- 145 (DSMZ Accession Number ACC 261, ATCC Accession Number HTB-81), or BM 1604 (DSMZ Accession Number ACC 298) cells. or that the heavy or light chain variable region has an insertion, deletion or substitution in one amino acid residue in either or both of SEQ ID NO:5 and SEQ ID NO:7. In this case, the claims do not require that the antibodies specifically bind to any particular antigen or necessarily comprise each of the 6 complementarity determining regions (CDRs) of the monoclonal antibody Norm-2, i.e., the CDRs<sup>1</sup> that are disclosed in the heavy chain variable domain of SEQ ID NO:5 and the light chain variable region of SEQ ID NO:7, wherein the antibody specifically binds the same antigen as the Norm-2 antibody produced by the cell line deposited as DSMZ accession number DSM ACC2626, nor do the claims require that the fragment be an antigen-binding fragment comprising each of the 6 complementarity determining regions (CDRs) of the monoclonal antibody Norm-2, i.e., the CDRs that are disclosed in the heavy chain variable domain of SEQ ID NO:5 and the light chain variable region of SEQ ID NO:7, wherein the antigen-binding fragment specifically binds the same antigen as the Norm-2 antibody produced by the cell line deposited as DSMZ accession number DSM ACC2626.

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<sup>1</sup> See page 3 of the specification for a disclosure of the CDR sequences present in SEQ ID NO:5 and 7

However, as will be explained in further detail in the following paragraphs, the specification only adequately describes isolated antibodies or antigen-binding fragments thereof, wherein the antibody or antigen-binding fragment thereof specifically binds the same antigen as the monoclonal antibody produced by the cell line deposited as DSMZ accession number DSM ACC2626, and wherein said antibody or said antigen-binding fragment thereof comprises: a heavy chain variable domain comprising a CDR1 comprising the amino acid sequence of amino acids 31-35 of SEQ ID NO:5, a CDR2 comprising the amino acid sequence of amino acids 50-66 of SEQ ID NO:5 and a CDR3 comprising the amino acid sequence of amino acids 99-108 of SEQ ID NO:5 and a light chain variable domain comprising a CDR1 comprising the amino acid sequence of amino acids 23-36 of SEQ ID NO:7, a CDR2 comprising the amino acid sequence of amino acids 52-58 of SEQ ID NO:7 and a CDR3 comprising the amino acid sequence of amino acids 91-101 of SEQ ID NO:7.

As an initial point, the specification fails to adequately describe the claimed antibodies or functional fragments thereof which have the function of specifically binding to an adenocarcinoma of the colon, a diffuse-type stomach carcinoma, an adenocarcinoma of the pancreas, or an adenocarcinoma of the lung because one of skill in the art could not immediately envision, recognize or predict, for example, which antibody that has heavy chain variable region with 95% identity to SEQ ID NO:5 would specifically bind to these cells from those that would not. In this case, the specification has not identified or characterized the antigen to which the monoclonal antibody designated Norm-2 specifically binds and therefore, the claims are not directed to antibodies that specifically bind to a well-characterized antigen. Cells of an adenocarcinoma of the colon, a diffuse-type stomach carcinoma, an adenocarcinoma of the pancreas, or an adenocarcinoma of the lung express multiple different antigens and, as will be explained in further detail below, by altering CDR residues of an antibody, the antigen to which an antibody binds can be altered. Accordingly, as it is well-established in the art that altering the amino acid sequence of an antibody by amino acid insertions, substitutions or deletions has greatly unpredictable results on antibody functions, such as antigen binding, one of skill in the art would not recognize that Applicant was in

possession of the claimed antibodies or functional fragments thereof unless antibodies comprise a heavy chain variable domain comprising the 3 heavy chain CDRs of the NORM-2 antibody and a light chain variable domain comprising the 3 light chain CDRs of the NORM-2 antibody which specifically bind to the same antigen as the monoclonal antibody produced by the cell line deposited as DSMZ accession number DSM ACC2626 or the fragment is an antigen-binding fragment thereof comprising the 3 heavy chain CDRs of the NORM-2 antibody and a light chain variable domain comprising the 3 light chain CDRs of the NORM-2 antibody which specifically bind to the same antigen as the monoclonal antibody produced by the cell line deposited as DSMZ accession number DSM ACC2626.

Notably, while the Federal Circuit has recently decided that the description of a fully characterized molecular target of an antibody is sufficient to adequately describe a genus of antibodies that binds that target (See *Noelle v. Lederman*, 69 USPQ2d 1508 (CA FC 2004)) the same court decided that each case involving the issue of written description, “must be decided on its own facts. Thus, the precedential value of cases in this area is extremely limited.” *Vas-Cath*, 935 F.2d at 1562 (quoting *In re Driscoll*, 562 F.2d 1245, 1250 (C.C.P.A. 1977)).

Following the example set by the Federal Circuit in deciding *Noelle v. Lederman*, then, were the claims directed to an antibody that binds a well-characterized antigen, the written description would be met. However, as explained above, the claims are not drawn to an antibody that binds a well-characterized antigen and the specification does not identify the antigen to which the monoclonal antibody designated NORM-2 specifically binds.

To elaborate on why the claimed antibodies and functional fragments lack adequate written description, Mariuzza et al. (*Annu. Rev. Biophys. Biophys. Chem.* 1987; **16**: 139-159) reviews the structural basis of antigen-antibody recognition and teaches that a naturally occurring antibody comprises two polypeptides, the so-called light and heavy chains. The antigen-combining site of an antibody is a three-dimensional structure, which fully comprises six “complementarity-determining regions”

(CDRs), three each from the light and heavy chains. The amino acid sequences of the CDRs are hypervariable, as the amino acid residues contained within the CDRs determine much of antibody's antigen-binding specificity. Of the amino acid residues of the antibody contacting the antigen, six are within the light chain, nine are within the heavy chain, and two are within the constant or nearly constant "framework" regions.

In view of Mariuzza et al., it is apparent that antibodies having less than all six CDRs that form the antigen binding site of an antibody in their proper context of heavy and light chain variable domains does not suffice to describe the particularly identifying structural feature of the antibody that correlates with the antibody's ability to bind to the antigen. Absent a description of the at least minimal structural features correlating with a functional ability to bind to a particular antigen, which are shared by members of a genus commonly sharing this function, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish members of the genus from other antibodies. For this reason, the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Notably, in this case, the specification only describes antibodies comprising 3 CDRs of a heavy chain in a heavy chain framework and three CDRs of a light chain in a light chain framework as antibodies or antigen binding fragments thereof comprising these 6 CDRs as molecules that specifically bind to the same antigen as the monoclonal antibody designated Norm-2 (see page 13 of the specification, lines 16-28, page 18, line 9 to page 19, line 9 and page 10). Since the specification does not characterize the antigen to the monoclonal antibody designated Norm-2 specifically binds, one of skill in the art could not immediately envision, recognize or predict if alterations in the CDRs of the monoclonal antibody designated Norm-2 would result in an antibody which bound the same antigen or not.

While the prior art teaches well-known and conventional methodology for "humanizing" monoclonal antibodies by CDR grafting heavy and light chain CDRs into corresponding human heavy and light chain frameworks to give an antibody that binds the same antigen as the parent antibody, one of skill in the art would not immediately

envision or recognize antibodies or functional fragments thereof comprising less than all 6 CDRs of a parent antibody in the proper context of heavy and light chain frameworks as retaining the binding affinity and specificity of the parent antibody and would not conclude that, for example, an antibody that binds to a diffuse-type stomach carcinoma cell, comprising completely different or altered CDR sequences would necessarily bind the same antigen as the parent antibody because cancer cells are known to express thousands of distinct antigens to which the antibody could bind.

For example, Gussow et al. (Methods in Enzymology. 1991; 203: 99-121) teach the general methodology for making humanized antibodies; see entire document. One means for producing a humanized antibody involves grafting the six CDRs from the light and heavy chain variable regions from a murine antibody into the framework of a human antibody. However, in general, if only one or two of the CDRs from either the light or heavy chain variable region were to be grafted, but not all three, the resultant antibody would not be expected to retain the binding affinity and specificity of the parent antibody. Therefore, since it is expected that all 6 CDRs need to be grafted into antibody framework regions to retain the requisite affinity and specificity of the parent antibody, fusion molecules comprising targeting portions that do not comprise all 6 CDRs grafted into framework regions, i.e., are not antibodies or antigen-binding fragments thereof that contain all 6 CDRs of the parent antibody, would not be immediately envisioned or recognized by one of skill in the art as having the affinity and specificity of the parent antibody.

Furthermore, while the prior art teaches some understanding of the structural basis of antigen-antibody recognition and conventional methodology for humanizing monoclonal antibodies, it is aptly noted that the art is characterized by a high level of unpredictability, since the skilled artisan still cannot accurately and reliably predict the consequences of amino acid substitutions, insertions, and deletions in the antigen-binding domains and surrounding framework regions of antibodies. For example, Giusti et al. (*Proc. Natl. Acad. Sci. USA*. 1987 May; **84** (9): 2926-2930) teaches the specificity and affinity of an antibody is exquisitely sensitive to amino acid substitutions within the primary structure of the antibody, since only a single amino acid substitution in the

Art Unit: 1643

heavy chain of an antibody completely altered the binding specificity of an antibody that binds phosphocholine, such that the altered antibody fails to bind phosphocholine but instead binds DNA; see entire document (e.g., the abstract). This unpredictability of single amino acid changes in an antibody is underscored by Winkler et al (J. Imm., 265:4505-4514, 2000) who teach that single amino acid changes in antibody side chains can result in unpredictable and substantial changes in antibody specificity; see entire document (e.g., the abstract). Chien et al. (*Proc. Natl. Acad. Sci. USA*. 1989 Jul; **86** (14): 5532-5536) teaches that significant structural and functional changes in an antigen-binding site can be caused by amino acid substitutions in the primary structure of an antibody, including substitutions at a site remote from the complementarity determining regions of the antigen-binding domain; see entire document (e.g., the abstract). Similarly, but more recently, Caldas et al. (*Mol. Immunol.* 2003 May; **39** (15): 941-952) teaches an unexpected effect of substituting a framework residue upon binding specificity during the humanization of an antibody that binds CD18; see entire document (e.g., the abstract).

The Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

Additionally, “generalized language may not suffice if it does not convey the detailed identity of an invention.” *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

The purpose of the “written description” requirement is broader than to merely explain how to “make and use”; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the “written description” inquiry, *whatever is now claimed*.

*Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

“Guidelines” states, “[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention” (*Id.* at 1104). Moreover, because the claims are directed to a genus of structurally disparate antibodies and functional fragments thereof, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was “ready for patenting” by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

It is not sufficient to define a substance solely by its principal biological property, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. Per the *Enzo* court's example, (*Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (CA FC 2002) at 1616) of a description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) couched “in terms of its function of lessening inflammation of tissues” which, the court stated, “fails to distinguish any steroid from others having the same activity or function”. Similarly, the function of binding to cells of an adenocarcinoma of the colon, a diffuse-type stomach carcinoma, an adenocarcinoma of the pancreas, or an adenocarcinoma of the lung or the functions of inducing apoptosis or decreasing proliferation of the recited cell lines does not distinguish antibodies or functional fragments thereof, from others having the same activity or function and as such, fails to satisfy the written-description requirement. Applicant has not disclosed any relevant,

identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed genus. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Given the lack of particularity with which the antibodies and functional fragments thereof, to which the claims are directed, are described in the specification, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish at least most of the members of the claimed genera, to which the claims are directed; and therefore the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

13. Claims 21-23, 28-32, 35, 47 and 89-95 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

As amended, claims 21-23, 28-32, 35, 47 and 89-95, recite the added limitation “wherein the antibody or functional fragment thereof specifically binds to an adenocarcinoma of the colon, a diffuse-type stomach carcinoma, an adenocarcinoma of the pancreas, or an adenocarcinoma of the lung”.

Applicant has indicated that support for this amendment can be found throughout the specification, but in particular in originally filed claim 33 at pages 2, lines 20-23 and at page 3, lines 19-22.

Contrary to Applicant's assertion, however, it does not appear that the specification, including the claims, as originally filed, provides written support for the language of the claims.

Notably both original claim 33 and the specification also recite that, in addition to binding these cancer cells, these products do not specifically bind "to a non-neoplastic cell of the same tissue type". Accordingly, the limitation that the antibody or functional fragment thereof specifically bind to an adenocarcinoma of the colon, a diffuse-type stomach carcinoma, an adenocarcinoma of the pancreas, or an adenocarcinoma of the lung appears to set forth a broader genus than originally contemplated in the specification because the claims, as amended, do not exclude antibodies that specifically bind to a non-neoplastic cell of the same tissue type.

Given the apparent difference in the breadth of the claims and that of the pertinent disclosures, it is submitted that the amendment has introduced new concepts, violating the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

Otherwise this issue might be resolved if Applicant were to point to other disclosures in the specification, including the claims, as originally filed, which are believed to provide the necessary written support for the language of the instant claims.

14. Claims 30, 47, 93 and 94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 30, 93 and 94 are directed to antibodies of functional fragments thereof which specifically bind, induce apoptosis or decrease proliferation of cell lines designated "Colo-699 (DSMZ Accession Number ACC 196), CACO-2 (DSMZ Accession Number ACC169, ATCC Accession Number HTB-37), 23132/87 (DSMZ Accession Number ACC 201), DU-145 (DSMZ Accession Number ACC 261, ATCC Accession Number HTB-81), or BM 1604 (DSMZ Accession Number ACC 298)".

It is unclear if the claimed Colo-699 (DSMZ Accession Number ACC 196), CACO-2 (DSMZ Accession Number ACC169, ATCC Accession Number HTB-37), 23132/87 (DSMZ Accession Number ACC 201), DU-145 (DSMZ Accession Number

Art Unit: 1643

ACC 261, ATCC Accession Number HTB-81), or BM 1604 (DSMZ Accession Number ACC 298) cells, are known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes or proof on the record that Colo-699 (DSMZ Accession Number ACC 196), CACO-2 (DSMZ Accession Number ACC169, ATCC Accession Number HTB-37), 23132/87 (DSMZ Accession Number ACC 201), DU-145 (DSMZ Accession Number ACC 261, ATCC Accession Number HTB-81), or BM 1604 (DSMZ Accession Number ACC 298) cells is suggested. Without a publicly available deposit of the above host cell lines, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of the claimed host cells is an unpredictable event.

While the specification contains deposit information for the claimed cell lines, the specification lacks proof the recited cell lines are publicly available. It is unclear whether Colo-699 (DSMZ Accession Number ACC 196), CACO-2 (DSMZ Accession Number ACC169, ATCC Accession Number HTB-37), 23132/87 (DSMZ Accession Number ACC 201), DU-145 (DSMZ Accession Number ACC 261, ATCC Accession Number HTB-81), or BM 1604 (DSMZ Accession Number ACC 298) possessing the identical properties of said cells are known and publicly available or can be reproducibly isolated from nature without undue experimentation.

Although the specification provides deposit information for the recited cell lines, this description does not indicate whether these cell lines are known and publicly available. It is unclear whether one of skill in the art would have access to said cell lines in order to be able to practice the invention as claimed. If these cell lines were not known and publicly available, undue experimentation would be required to reproduce these cell lines.

Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the claimed cell lines, a suitable deposit is required for patent purposes, evidence of public availability of the claimed antibody or evidence of the reproducibility without undue experimentation of the claimed antibody, is required.

If Applicant makes a deposit of these cells lines under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit of the Raji cells or Namalwa cells has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that the deposit will be replaced if viable samples cannot be dispensed by the depository, that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application and access to the deposit will be available during pendency of the patent application making reference to the deposit to one determined by the Commissioner to be entitled thereto under 37 CFR 1.14 and 35 U.S.C. 122 is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves these specific matters to the discretion of each State.

If the deposit of the cell lines is not made under the provisions of the Budapest Treaty, then in order to certify that the deposit complies with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

- (a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;
- (b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;
- (c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and
- (d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed. See MPEP 2406 and 37 CFR 1.804(b).

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Secondly, with respect to claim 47, although indefinite for the reasons set forth above, the claim recites the "NORM-2 cell line having DSMZ deposit accession number DSM ACC2626".

It is unclear if a NORM-2 cell line having DSMZ deposit accession number DSM ACC2626, possessing the identical properties of the disclosed NORM-2 cell line is known and publicly available or can be reproducibly isolated from nature without undue experimentation.

Although the specification provides deposit information for the Norm 2 cell line and identifies that this deposit was made under the Budapest treaty (see page 19, lines 4-9), this description does not meet all the conditions of 37 CFR 1.801-1.809. Accordingly, it is unclear whether one of skill in the art would have access to said cells lines in order to be able to practice the invention as claimed. If this cell line was not known and publicly available, undue experimentation would be required to reproduce this cell line.

As the deposit was made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit of the Norm-2 cell line deposited as DSMZ accession number ACC2626 has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that the deposit will be replaced if viable samples cannot be dispensed by the depository, that all

Art Unit: 1643

restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application and access to the deposit will be available during pendency of the patent application making reference to the deposit to one determined by the Commissioner to be entitled thereto under 37 CFR 1.14 and 35 U.S.C. 122 is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves these specific matters to the discretion of each State.

Applicant's attention is directed to *In re Lundak*, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

15. Claims 21-23, 27-32, 35, 47 and 89-96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** isolated antibodies or antigen-binding fragments thereof, wherein the antibody or antigen-binding fragment thereof specifically binds the same antigen as the monoclonal antibody produced by the cell line deposited as DSMZ accession number DSM ACC2626, and wherein said antibody or said antigen-binding fragment thereof comprises: a heavy chain variable domain comprising a CDR1 comprising the amino acid sequence of amino acids 31-35 of SEQ ID NO:5, a CDR2 comprising the amino acid sequence of amino acids 50-66 of SEQ ID NO:5 and a CDR3 comprising the amino acid sequence of amino acids 99-108 of SEQ ID NO:5 and a light chain variable domain comprising a CDR1 comprising the amino acid sequence of amino acids 23-36 of SEQ ID NO:7, a CDR2 comprising the amino acid sequence of amino acids 52-58 of SEQ ID NO:7 and a CDR3 comprising the amino acid sequence of amino acids 91-101 of SEQ ID NO:7, *provided* the deposit requirements are first met for the cell line deposited as DSMZ accession number DSM ACC2626, **and while being enabling for making and using** any antibodies or functional fragments thereof encompassed by the claims, which have been described by the prior art, **does not reasonably provide enablement for making and using** the full scope of the claimed antibodies and functional fragments thereof. The specification does not enable any person skilled in the art to which it

Art Unit: 1643

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

MPEP § 2164.01 states:

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

The claims are drawn to antibodies or functional fragments thereof, such as an antibody comprising a heavy chain variable region with at least 80% identity to the amino acid sequence of SEQ ID NO:5 and a light chain variable region with at least 80% identity to the amino acid sequence of SEQ ID NO:7, wherein the antibody specifically binds to an adenocarcinoma of the colon, a diffuse-type stomach carcinoma,

an adenocarcinoma of the pancreas, or an adenocarcinoma of the lung, or a functional fragment thereof which specifically binds to an adenocarcinoma of the colon, a diffuse-type stomach carcinoma, an adenocarcinoma of the pancreas, or an adenocarcinoma of the lung (see claim 21) or an antibody comprising amino acids 31-35, 50-66, and 99-108 of SEQ ID NO:5 or amino acids 23-36, 52-58, and 91-101 of SEQ ID NO:7 or a functional fragment thereof. Notably, because claim 32 recites that said functional fragment of claim 21 or claim 27 can be an Fc domain, which would not comprise a variable light chain domain or a variable heavy chain domain, it is apparent that the "functional fragment thereof" of claim 21 and claim 27 is not required to comprise any amino acid sequence of SEQ ID NO:5 or 7. Further dependent claims set forth other percent identities that the antibody must have to SEQ ID NO:5 and/or 7 (see claims 22, 23, 89, 90, 91 and 92) that the antibody or functional fragment thereof induce apoptosis (claim 93) or decreases proliferation (claim 94) of any one of Colo-699 (DSMZ Accession Number ACC 196), CACO-2 (DSMZ Accession Number ACC169, ATCC Accession Number HTB-37), 23132/87 (DSMZ Accession Number ACC 201), DU- 145 (DSMZ Accession Number ACC 261, ATCC Accession Number HTB-81), or BM 1604 (DSMZ Accession Number ACC 298) cells or that the heavy or light chain variable region has an insertion, deletion or substitution in one amino acid residue in either or both of SEQ ID NO:5 and SEQ ID NO:7 (see claims 95-96). However, the claims do not require that the antibodies specifically bind to any particular antigen or necessarily comprise each of the 6 complementarity determining regions (CDRs) of the monoclonal antibody Norm-2, i.e., the CDRs that are disclosed in the heavy chain variable domain of SEQ ID NO:5 and the light chain variable region of SEQ ID NO:7, wherein the antibody specifically binds the same antigen as the Norm-2 antibody produced by the cell line deposited as DSMZ accession number DSM ACC2626.

As a first point, since the claims are not limited to antibodies or antigen-binding fragments thereof that specifically bind to one well-characterized antigen, but either entirely lack antigen-binding function, see e.g., claim 27, or specifically bind to an adenocarcinoma of the colon, a diffuse-type stomach carcinoma, an adenocarcinoma of the pancreas, or an adenocarcinoma of the lung, see e.g., claim 21, one of skill in the

Art Unit: 1643

art would be subject to undue and unreasonable experimentation to make and use the claimed antibodies. For example, since adenocarcinomas of the colon, diffuse-type stomach carcinomas, adenocarcinomas of the pancreas, or adenocarcinomas of the lung, express thousands of different antigens, but monoclonal antibodies, like the disclosed NORM-2 antibody which comprises a heavy chain variable domain comprising SEQ ID NO:5 and a light chain variable domain comprising SEQ ID NO:7, only specifically bind to one antigen, one of skill in the art would be subject to undue experimentation to make antibodies comprising the claimed structural features that bind to an antigen other than the antigen specifically bound by the Norm-2 antibody produced by the cell line deposited as DSMZ accession number DSM ACC2626. In this case, the specification provides no specific, non-general guidance as to which amino acids might be altered in the NORM-2 antibody to change its antigen-binding specificity for any other antigen, and as will be explained in further detail below, amino acid alterations in an antibody made relative to a parent antibody have highly unpredictable effects on antigen-binding specificity. For these reasons, one of skill in the art would be subject to undue experimentation to make antibodies commensurate to the full scope of the claimed invention.

Furthermore, while the specification teaches one of skill in the art how to use an antibody or antigen-binding fragment thereof specifically binds the same antigen as the monoclonal antibody produced by the cell line deposited as DSMZ accession number DSM ACC2626, wherein said antibody or said antigen-binding fragment thereof comprises: a heavy chain variable domain comprising a CDR1 comprising the amino acid sequence of amino acids 31-35 of SEQ ID NO:5, a CDR2 comprising the amino acid sequence of amino acids 50-66 of SEQ ID NO:5 and a CDR3 comprising the amino acid sequence of amino acids 99-108 of SEQ ID NO:5 and a light chain variable domain comprising a CDR1 comprising the amino acid sequence of amino acids 23-36 of SEQ ID NO:7, a CDR2 comprising the amino acid sequence of amino acids 52-58 of SEQ ID NO:7 and a CDR3 comprising the amino acid sequence of amino acids 91-101 of SEQ ID NO:7 because the NORM-2 antibody specifically binds to an antigen expressed on colon, stomach, pancreas and lung adenocarcinomas, but not normal colon, stomach,

Art Unit: 1643

pancreas and lung tissue (see page 50-51), since other antigens are not necessarily differentially expressed on colon, stomach, pancreas and lung adenocarcinomas, one of skill in the art would be subject to undue experimentation to identify a use for antibodies that bind a different antigen than the NORM-2 antibody.

Furthermore, the specification does not enable functional fragments of antibodies or antibodies comprising less than a heavy chain variable domain comprising a CDR1 comprising the amino acid sequence of amino acids 31-35 of SEQ ID NO:5, a CDR2 comprising the amino acid sequence of amino acids 50-66 of SEQ ID NO:5 and a CDR3 comprising the amino acid sequence of amino acids 99-108 of SEQ ID NO:5 and a light chain variable domain comprising a CDR1 comprising the amino acid sequence of amino acids 23-36 of SEQ ID NO:7, a CDR2 comprising the amino acid sequence of amino acids 52-58 of SEQ ID NO:7 and a CDR3 comprising the amino acid sequence of amino acids 91-101 of SEQ ID NO:7 because one of skill in the art would be subject to undue experimentation to make antibodies comprising amino acid alterations in the CDRs as compared to the CDRs in the parent NORM-2 antibody, which would bind to the same antigen as this parent antibody. Notably, the specification does not provide any specific, non-general guidance as to which CDR residues could be predictably altered to retain the antigen-binding specificity of the NORM-2 antibody.

As noted by Mariuzza et al. (*supra*), it is well established fact in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable domains of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid

Art Unit: 1643

sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA 1982 Vol. 79: page 1979). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibodies that do not contain all of the 6 CDRs of the parent NORM-2 antibody in their proper context of heavy and light chain variable domains, respectively, would retain the binding function of the parent antibody. For example, as set forth in the above rejection of the claims as lacking adequate written description, Gussow et al (*supra*) teaches conventional methodologies for “humanizing” monoclonal antibodies which generally involve grafting the six CDRs from the light and heavy chain variable regions from a murine antibody into the framework of a human antibody. However, in general, if only one or two of the CDRs from the light and heavy chain variable region were to be grafted, but not all three, the resultant antibody would not be expected to retain the binding affinity and specificity of the parent antibody.

Thus, while the prior art teaches some understanding of the structural basis of antigen-antibody recognition and conventional methodology for humanizing monoclonal antibodies, it is aptly noted that the art is characterized by a high level of unpredictability, since the skilled artisan still cannot accurately and reliably predict the consequences of amino acid substitutions, insertions, and deletions in the antigen-binding domains and surrounding framework regions of antibodies. For example, Giusti et al. (*supra*) teaches the specificity and affinity of an antibody is exquisitely sensitive to amino acid substitutions within the primary structure of the antibody, since only a single amino acid substitution in the heavy chain of an antibody completely altered the binding specificity of an antibody that binds phosphocholine, such that the altered antibody fails to bind phosphocholine but instead binds DNA; see entire document (e.g., the abstract). Chien et al. (*supra*) teaches that significant structural and functional changes in an antigen-binding site can be caused by amino acid substitutions in the primary structure of an antibody, including substitutions as a site remote from the complementarity

Art Unit: 1643

determining regions of the antigen-binding domain; see entire document (e.g., the abstract). Similarly, but more recently, Caldas et al. (*supra*) teaches an unexpected effect of substituting a framework residue upon binding specificity during the humanization of an antibody that binds CD18; see entire document (e.g., the abstract).

The art of engineering functional recombinant antibodies, such as those to which the claims are directed, is even more confounded by findings that residues, which are positioned outside the recognized boundaries of the canonical CDRs, may contribute substantially to the interaction of an antibody and an antigen. For example, MacCallum et al. (*J. Mol. Biol.* 1996 Oct 11; **262** (5): 732-745) describes the discovery that although the residues of CDR3 of the heavy and light chains are dominant determinants of the interaction, a number of essential residues contacting the antigen have been placed outside the regions that are recognized using the conventional or standard definitions of the CDRs, which are generally used to define the components of the antigen binding site of the antibody; see entire document (e.g., page 733, column 2). Moreover, MacCallum et al. teaches an appreciation of the fact that residues within the CDRs that do not actually make contact with the antigen may be important because of their contributions to the conformation of the antibody's antigen recognition site; see, e.g., page 735, column 1.

Making further apparent the unpredictability of the importance of residues within the CDRs and other parts of an antibody, which must instead be determined empirically, Holm et al. (*Mol. Immunol.* 2007 Feb; **44** (6): 1075-1084) describes the mapping of residues important to the interaction of an anti-cytokeratin antibody with the antigen, where although residues in the CDR3 of the heavy chain were determined to be essential, they disclose their *unexpected* finding that a residue in CDR2 of the light chain forms a necessary part of the antigen binding site of the antibody contacting the antigen; see entire document (e.g., the abstract). Thus, as recently as 2007, there are reports indicating despite the progress made toward understanding the interactions of antibodies and antigens, because of the unpredictable nature of the art, much information concerning the specificity and/or affinity of any given antibody cannot be gleaned by routine and conventional experimentation, but instead must be gathered by

Art Unit: 1643

rigorous and undue experimentation. For these reasons, one of skill in the art would be subject to undue and unreasonable experimentation to make antibodies commensurate in scope with the claimed antibodies which would bind to the same antigen as the NORM-2 monoclonal antibody.

As noted above, none of the claims currently recite specifically binding to the same antigen as the monoclonal antibody produced by the cell line deposited as DSMZ accession number DSM ACC2626. However, since the specification does not identify the antigen bound by the NORM-2 monoclonal antibody produced by the cell line deposited as DSMZ accession number DSM ACC2626, one of skill in the art would need this antibody so they could predictably make and use the invention without undue experimentation. Notably, if the cell line deposited as DSMZ accession number DSM ACC2626 producing the NORM-2 antibody was publicly available, it would be routine in the art to purify the antigen bound by this antibody and this purified antigen could then be routinely used to make and use isolated antibodies or antigen-binding fragments thereof, wherein the antibody or antigen-binding fragment thereof specifically binds the same antigen as the monoclonal antibody produced by the cell line deposited as DSMZ accession number DSM ACC2626, and wherein said antibody or said antigen-binding fragment thereof comprises: a heavy chain variable domain comprising a CDR1 comprising the amino acid sequence of amino acids 31-35 of SEQ ID NO:5, a CDR2 comprising the amino acid sequence of amino acids 50-66 of SEQ ID NO:5 and a CDR3 comprising the amino acid sequence of amino acids 99-108 of SEQ ID NO:5 and a light chain variable domain comprising a CDR1 comprising the amino acid sequence of amino acids 23-36 of SEQ ID NO:7, a CDR2 comprising the amino acid sequence of amino acids 52-58 of SEQ ID NO:7 and a CDR3 comprising the amino acid sequence of amino acids 91-101 of SEQ ID NO:7.

It is unclear if a cell line (e.g., a hybridoma) that produces an antibody having the exact structural and chemical identity as the monoclonal antibody designated "NORM-2" is known and publicly available, or can be reproducibly isolated without undue experimentation. Without access to a hybridoma or recombinant cell line producing the

Art Unit: 1643

monoclonal antibodies, it would not be possible to make and/or use the claimed invention, because it would not be possible to make the antibody.

For example, very different VH chains (about 50% homologous) can combine with the same VK chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different VH sequences combine with different VK sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementary-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY page 242 (William E. Paul, M.D. ed., 3d ed; 1993)]. Therefore, it would require undue experimentation to reproduce the designated cell line.

Although the specification provides deposit information for the Norm-2 cell line and identifies that this deposit was under the Budapest treaty (see page 19, lines 4-9), this description does not meet all the conditions of 37 CFR 1.801-1.809. As the deposit was made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit of the Norm-2 cell line deposited as DSMZ accession number ACC2626 has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that the deposit will be replaced if viable samples cannot be dispensed by the depository, that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application and access to the deposit will be available during pendency of the patent application making reference to the deposit to one determined by the Commissioner to be entitled thereto under 37 CFR 1.14 and 35 U.S.C. 122 is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves these specific matters to the discretion of each State.

Applicant's attention is directed to *In re Lundak*, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

If the deposit requirements were satisfied, the disclosure would be sufficient to make and use isolated antibodies or antigen-binding fragments thereof, wherein the antibody or antigen-binding fragment thereof specifically binds the same antigen as the monoclonal antibody produced by the cell line deposited as DSMZ accession number DSM ACC2626, and wherein said antibody or said antigen-binding fragment thereof comprises: a heavy chain variable domain comprising a CDR1 comprising the amino acid sequence of amino acids 31-35 of SEQ ID NO:5, a CDR2 comprising the amino acid sequence of amino acids 50-66 of SEQ ID NO:5 and a CDR3 comprising the amino acid sequence of amino acids 99-108 of SEQ ID NO:5 and a light chain variable domain comprising a CDR1 comprising the amino acid sequence of amino acids 23-36 of SEQ ID NO:7, a CDR2 comprising the amino acid sequence of amino acids 52-58 of SEQ ID NO:7 and a CDR3 comprising the amino acid sequence of amino acids 91-101 of SEQ ID NO:7.

Applicant is reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify other antibodies that are encompassed by the claims; yet, defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any

Art Unit: 1643

material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

In conclusion, upon careful and full consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enabled the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation, and this rejection is being maintained.

### ***Claim Rejections - 35 USC § 102***

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

17. Claims 21, 27, 30, 31, 32, 47 and 95 are rejected under 35 U.S.C. 102(b) as being anticipated by Immunobiology 5 (Edited by Janeway et al, pages 96-97, 2001) as evidenced by Kettunen et al (C. Gen. Cyto., 149:98-106, 2004).

The claims are herein interpreted as being drawn to a functional fragment of an antibody, such as an Fc fragment. Notably, claim 32 specifically claims an Fc fragment as a functional fragment of an antibody of claim 21. Furthermore, since Fc fragments do not comprise variable domains comprising, e.g., the variable domain sequences of

SEQ ID NO:5 and/or SEQ ID NO:7, it is apparent that the functional fragments recited in claim 21 and 27 should be broadly, but reasonably interpreted to include functional fragments that do not comprise any of the recited variable domain sequences, such as an Fc fragment. This is in contrast to other claims that are not included in this rejection, which recite wherein clauses that limit the functional fragment to comprise some part of the amino acid sequence of SEQ ID NO:5 and/or 7 (see e.g., claim 22 which recites the phrase “wherein said polypeptide antibody or a functional fragment thereof comprises a heavy chain variable region with at least 85% identity to the amino acid sequence of SEQ ID NO:5”. Furthermore, although indefinite for the reason detailed above, claim 47 is being included in this rejection because Fc fragments could be obtained from the recited cell line which produces a monoclonal antibody as well as producing numerous polypeptides. Finally, claim 21 requires that the functional fragment thereof specifically bind to an adenocarcinoma of the colon, a diffuse-type stomach carcinoma, an adenocarcinoma of the pancreas, or an adenocarcinoma of the lung, and claim 30 designates a lung adenocarcinoma as Colo-699. Notably, as evidenced by Kettunen et al, adenocarcinomas of the lung express the Fc receptor, FcRn, and this receptor specifically binds to the Fc domain of IgG antibodies.

Immunobiology 5 (Edited by Janeway et al, pages 96-97, 2001 teaches that antibodies, such as IgG antibodies, comprise numerous fragments including a Fc fragment that is produced by papain cleavage of the antibody (see entire document, e.g., page 96). Accordingly, this Fc fragment is materially and structurally indistinguishable from the instantly claimed Fc fragment, regardless of how the product is produced. Therefore, absent a showing of any difference, the claimed Fc fragment and the Fc fragment disclosed by the prior art are deemed the same and Immunobiology 5 anticipate the claimed invention.

18. Claims 21-23, 27-31, 35, 47 and 89-96 are rejected under 35 U.S.C. 102(b) as being anticipated by Vollmers et al (Cell, 40:547-557, 1985, IDS filed 3/16/2007).

The claims are herein drawn to an antibody comprising amino acids 31-35, 50-66, and 99-108 of SEQ ID NO:5 and amino acids 23-36, 52-58, and 91-101 of SEQ ID

NO:7, such as the NORM-2 monoclonal antibody (see page 18, lines 9-16) or an antibody comprising a deletion of one amino acid in the amino acid sequence of SEQ ID NO:5 and/or SEQ ID NO:7, such as the NORM-2 monoclonal antibody. Notably, when an amino acid is deleted from either end of the amino acid sequence of SEQ ID NO:5, one obtains an amino acid sequence that is still comprised in the NORM-2 antibody, i.e., the NORM-2 antibody comprises SEQ ID NO:5 which is 108 amino acids in length and also comprises the amino acid sequence of amino acids 1-107 of SEQ ID NO:5, wherein the amino acid sequence of amino acids 1-107 of SEQ ID NO:5 is considered a deletion of one amino acid in SEQ ID NO:5.

Vollmers et al., which shares an inventor in common with the instant application, teaches a NORM-2 monoclonal antibody (see entire document, e.g., abstract). While, Vollmers et al., do not expressly teach that the disclosed NORM-2 monoclonal antibody has the same properties as the instantly claimed antibody, it is reasonable to conclude that an antibody designated NORM-2 in the prior art which is disclosed in a publication with an inventor in common with the instant application inherently comprises the same amino acid sequence and has the same properties as the instantly recited antibodies. “[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art’s functioning, does not render the old composition patentably new to the discoverer.” *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). In *In re Crish*, 393 F.3d 1253, 1258, 73 USPQ2d 1364, 1368 (Fed. Cir. 2004), the court held that the claimed promoter sequence obtained by sequencing a prior art plasmid that was not previously sequenced was anticipated by the prior art plasmid which necessarily possessed the same DNA sequence as the claimed oligonucleotides. The court stated that “just as the discovery of properties of a known material does not make it novel, the identification and characterization of a prior art material also does not make it novel.” *Id.* See MPEP § 2112. Notably, the Office lacks the resources and facilities to compare the antibody disclosed by the prior art and

the claimed antibody to establish whether there are any differences. Consequently, in the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed antibody is different than that taught by the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977); and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

In summary, the antibodies of the prior art are materially and structurally indistinguishable from the instantly claimed antibodies. Therefore, absent a showing of any difference, the claimed antibodies and the antibodies disclosed by the prior art are deemed the same.

19. Claims 21-23, 27-31, 35, 47 and 89-96 are rejected under 35 U.S.C. 102(a) as being anticipated by Brandlein et al (Can., Res., 7995-8005, 2003, IDS filed 3/16/2007).

The claims are herein drawn to an antibody comprising amino acids 31-35, 50-66, and 99-108 of SEQ ID NO:5 and amino acids 23-36, 52-58, and 91-101 of SEQ ID NO:7, such as the NORM-2 monoclonal antibody (see page 18, lines 9-16) or an antibody comprising a deletion of one amino acid in the amino acid sequence of SEQ ID NO:5 and/or SEQ ID NO:7, such as the NORM-2 monoclonal antibody. Notably, when an amino acid is deleted from either end of the amino acid sequence of SEQ ID NO:5, one obtains an amino acid sequence that is still comprised in the NORM-2 antibody, i.e., the NORM-2 antibody comprises SEQ ID NO:5 which is 108 amino acids in length and also comprises the amino acid sequence of amino acids 1-107 of SEQ ID NO:5, wherein the amino acid sequence of amino acids 1-107 of SEQ ID NO:5 is considered a deletion of one amino acid in SEQ ID NO:5.

Brandlein et al., which shares inventors in common with the instant application, teaches a NORM-2 monoclonal antibody (see entire document, e.g., page 7999). While, Brandlein et al., do not expressly teach that the disclosed NORM-2 monoclonal antibody has the same properties as the instantly claimed antibody, it is reasonable to conclude that an antibody designated NORM-2 in the prior art which is disclosed in a publication with inventors in common with the instant application inherently comprises the same amino acid sequence and has the same properties as the instantly recited

antibodies “[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art’s functioning, does not render the old composition patentably new to the discoverer.” *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). In *In re Crish*, 393 F.3d 1253, 1258, 73 USPQ2d 1364, 1368 (Fed. Cir. 2004), the court held that the claimed promoter sequence obtained by sequencing a prior art plasmid that was not previously sequenced was anticipated by the prior art plasmid which necessarily possessed the same DNA sequence as the claimed oligonucleotides. The court stated that “just as the discovery of properties of a known material does not make it novel, the identification and characterization of a prior art material also does not make it novel.” *Id.* See MPEP § 2112. Notably, the Office lacks the resources and facilities to compare the antibody disclosed by the prior art and the claimed antibody to establish whether there are any differences. Consequently, in the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed antibody is different than that taught by the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977); and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

In summary, the antibodies of the prior art are materially and structurally indistinguishable from the instantly claimed antibodies. Therefore, absent a showing of any difference, the claimed antibodies and the antibodies disclosed by the prior art are deemed the same.

20. Claims 21-23, 30, 31, 32, 89, 90 and 92-95 are rejected under 35 U.S.C. 102(e) as being anticipated by US patent 7,285,269 (Babcook et al, published 2007).

The claims are herein drawn to an isolated monoclonal antibody or a functional fragment thereof comprising a heavy chain variable region with at least 90% identity to the amino acid sequence of SEQ ID NO:5 and a light chain variable region with at least 95% identity to the amino acid sequence of SEQ ID NO:7, and wherein the antibody or

Art Unit: 1643

functional fragment thereof specifically binds to an adenocarcinoma of the colon, a diffuse-type stomach carcinoma, an adenocarcinoma of the pancreas, or an adenocarcinoma of the lung (see e.g., claim 21) or wherein said antibody or functional fragment induces apoptosis (claim 93) or reduces proliferation (claim 94) of any one of Colo-699 (DSMZ Accession Number ACC 196), CACO-2 (DSMZ Accession Number ACC169, ATCC Accession Number HTB-37), 23132/87 (DSMZ Accession Number ACC 201), DU- 145 (DSMZ Accession Number ACC 261, ATCC Accession Number HTB-81), or BM 1604 (DSMZ Accession Number ACC 298) cells. Claim 32 is herein drawn to an Fab, Fab' or and F(ab')<sub>2</sub> fragment of said antibody.

US Patent 7,285,269 teaches making isolated antibodies comprising a heavy chain variable region with at least 90% identity to the amino acid sequence of SEQ ID NO:5 and a light chain variable region with at least 95% identity to the amino acid sequence of SEQ ID NO:7 and making Fab, Fab' or and F(ab')<sub>2</sub> fragments of said antibodies (see entire document, e.g., columns 3-6). Notably, US patent 7,285,269 teaches antibodies comprising the light chain variable domain comprising the amino acid sequence of SEQ ID NO:304, which is 98.1% identical to the instantly recited SEQ ID NO:5 (see Exhibit A attached) and comprising the heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:158, which is 91.7% identical to the instantly recited SEQ ID NO:5. Furthermore, claim 95 is being included in this rejection because the claim recites that the heavy or light chain has, i.e., comprises, an insertion, deletion or substitution of one amino acid residue. Accordingly, because the heavy chain and light chain variable domains taught by US patent 7,285,269 are not 100% identical to the instantly recited heavy or light chain variable domains, respectively, one of skill in the art would broadly, but reasonably conclude that the prior art antibodies comprise one amino acid insertion, deletion or substitution. Finally, while US Patent 7,285,269 does not expressly teach said antibody binds to binds to an adenocarcinoma of the colon, a diffuse-type stomach carcinoma, an adenocarcinoma of the pancreas, or an adenocarcinoma of the lung or wherein said antibody or functional fragment induces apoptosis or reduces proliferation of any one of Colo-699 (DSMZ Accession Number

ACC 196), CACO-2 (DSMZ Accession Number ACC169, ATCC Accession Number HTB-37), 23132/87 (DSMZ Accession Number ACC 201), DU- 145 (DSMZ Accession Number ACC 261, ATCC Accession Number HTB-81), or BM 1604 (DSMZ Accession Number ACC 298) cells the antibody of the prior art is materially and structurally indistinguishable from the instantly claimed antibody. Therefore, absent a showing of any difference, the claimed antibodies and Fab, Fab' or and F(ab')<sub>2</sub> fragments thereof and the antibodies and Fab, Fab' or and F(ab')<sub>2</sub> fragments thereof disclosed by the prior art are deemed the same and US Patent 7,285,269 anticipates the claimed invention.

### ***Conclusion***

21. No claims are allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:30 PM, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

Art Unit: 1643

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,  
Brad Duffy  
571-272-9935

/Stephen L. Rawlings/  
Primary Examiner, Art Unit 1643

/bd/  
Examiner, Art Unit 1643  
July, 16, 2008